Patent
Attorney's Docket No. 016800-111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Yann MAHE et al.	)	Group Art Unit: 1806
	)	
Application No.: 08/716,531	)	Examiner: S. Huff
	)	
Filed: September 19, 1996	)	
	)	
For: PHARMACEUTICAL/COSMETIC COMPOSITIONS COMPRISING THE LYSINE-D-PROLINE-VALINE...	)	

DECLARATION PURSUANT TO 37 C.F.R. §1.132
BY YANN MAHE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Yann Mahe, declare and state that:

(1) I am a citizen of France, and reside at 36, Avenue de L'Epargne, 91390 Morsang Sur Orge, France.

(2) I have been employed by L'Oréal from 1992 to the present date. My current title is Head, Inflammation Research Unit, Hair Research Group.

(3) I was awarded a Ph.D. degree in Pharmacology from the University of Paris VI. My Curriculum Vitae is attached hereto.

(4) I have substantial expertise in the field of inflammation and pro-inflammatory cytokines.

(5) I have reviewed the prior art rejections cited by the Examiner during prosecution of this application for which I am an inventor. Based thereon, it is my

understanding that the Examiner has maintained her position that Oluyomi et al, *Eur. J. Pharmacol.*, 258:131-138 (1994), would suggest the use of Lys-D-Pro-Val, or compounds containing such tripeptide, to inhibit inflammation. Based on the following, I respectfully disagree with the Examiner's conclusion.

(6) I have carefully read Oluyomi et al (*Id.*). Based on this review, it is my opinion that this reference purports that Lys-D-Pro-Val and related analogs and peptides may be used as an antinociceptive or analgesic agents. In other words, the authors suggest the use of this and related peptides to inhibit pain. This is apparent, e.g., based on the title of the reference "Antinociceptive activity of peptides...Lys-Pro-Thr", the abstract, and the reference in its entirety. The authors base their conclusions on disclosed assays for evaluating the degree of antinociceptive (disclosed at section 2.2, page 132 of the reference).

(7) However, in my opinion this reference would not fairly suggest that this tripeptide would inhibit inflammation and pro-inflammatory cytokine release. With respect to my conclusion, I have noted page 137, Col. 1, lines 1-8, of the reference, which the Examiner indicates supports her view that the reference suggests the anti-inflammatory activity of such peptide. However, I respectfully disagree with the Examiner's conclusion.

(8) At the outset, I would note that this particular section of Oluyomi et al (*Id.*) is not artfully drafted. Indeed, unless carefully read, it would seemingly suggest that Hiltz and Lipton (1984) and (1991) had reported the anti-inflammatory effect of some peptides including Lys-D-Pro-Val-NH_2. However, upon a careful reading of Oluyomi et

al together with Hiltz (1989) and (1991) it is apparent that this reference would not suggest to one of ordinary skill the anti-inflammatory activity of Lys-D-Pro-Val. Moreover, in my opnion, it is absolutely necessary that Oluyomi et al be read together with the Hiltz (1989) and/or (1991) references, as these references are where Oluyomi et al derives their only factual support, and form their conclusions as to the effects of various peptides related to MSH on inflammation.

(9) Upon review of the Hiltz (1991) reference (earlier provided to the Examiner), it can be clearly appreciated that the authors found that Lys-D-Pro-Val-NH_2 was inactive, i.e., did not inhibit inflammation. This is clear, e.g., based on the abstract. This is further clear from the results at page 769 of the reference, and Figure 3, which show that Ac-D-Val^{13} α-MSH(11-13)-NH_2 significantly inhibited inflammation, whereas Ac-Lys-D-Pro-Val-NH_2 did not. Indeed, based on their results, Hiltz et al concluded that the presence of L-Pro was essential for retention of anti-inflammation activity. In fact, they expressly state in their abstract, at page 767, that "L-Pro^{12} is essential for the anti-inflammatory activity of Ac-α-MSH(11-13)-NH_2, whereas the L-Lys^{11} is not". (Emphasis supplied.)

(10) Moreover, in my opinion, the reasonable expectation that the L-Pro would have been required for anti-inflammatory activity is further supported by other references discussed by Hiltz et al (1991), in particular Ferreira et al, *Nature*, 334:698-700 (1988), and Eberle et al "The Melanotropins: Chemistry, Physiology, and Mechanisms of Action", Basal Karger, 1988, which the authors state similarly suggest the significance of the L-Pro residue on activity of α-MSH derived peptides.

(11) Therefore, in my expert opinion, one skilled in the art in possession of Oluyomi et al (*Id.*) would interpret this reference based on the state of the art, including Hiltz et al (1989) and (1991), and conclude that a Lys-D-Pro-Val containing compound would be expected not to function as an effective anti-inflammatory agent given the absence of the supposedly essential L-Pro residue. Quite surprisingly, and not suggested by the prior art, it was found by the present inventors that this residue (L-Pro) is not required for anti-inflammatory function. In particular, I am of the opinion that this result is contraindicated by Oluyomi et al (*Id.*), when this reference is properly interpreted.

(12) I am further of the opinion that it can not be reasonably extrapolated that a compound which inhibits pain, i.e., a compound which functions as an analgesic or antinociceptive, will necessarily also inhibit inflammation. While the Examiner is correct that some compounds that inhibit pain also inhibit inflammation, many do not. Moreover, even if there existed such a reasonable correlation, such a reasonable correlation would not exist herein with respect to the potential anti-inflammatory activity of the subject Lys-D-Pro-Val. Such a reasonable expectation could not exist with respect to the subject therapeutic based on its earlier reported antinociceptive activity, since the prior art, in particular Oluyomi et al (1994) when properly construed together with Hiltz (1989) and (1991), and other prior art references discussed above, would have suggested that such tripeptide would mediate no anti-inflammatory activity because it lacks a supposed "essential" L-Pro residue.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

July 29th, 1998
Date

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Publications:

1) **Y Mahé,** F Garcia-Romeu & R Motais : Inhibition by amiloride of both adenylate cyclase activity and the Na^+/H^+antiporter in fish erythrocytes. European J. Pharmacol. (**1985**) 116, 199-206.

2) H Wakasugi, L Rimsky, **Y Mahé**, A M Kamel, D Fradelizi, T Tursz & J Bertoglio: Epstein-Barr Virus-containing B-cell line produces an Interleukin-1 that it uses as a growth factor. Proc. Natl. Acad. Sci *USA* (**1987**) 84, 804-808.

3) H Wakasugi, C Bensimon, **Y Mahé**, P Busson, L Rimsky, D Fradelizi, J. Bertoglio & T Tursz : B cell-derived Interleukin 1(IL-1). Annales d'Immunologie de l'Institut Pasteur (**1987**) 138, 599-603.

4) T Tursz, C Bensimon, P Busson, **Y Mahé** & H Wakasugi: Production of IL-1 by EBV-infected cells. in Lymphocytes activation and differentiation. Mani & Dornand Eds. Walter de Gruyter Publ.; Berlin/New York (**1988**) 191-200.

5) H Wakasugi, **Y Mahé**, S Huet, L Boumsell, A Bernard & T Tursz: Comparison of signals delivered through CD3 and CD2 for T-cell activation: The role of calcium influx and Interleukin-1. Human Immunology (**1988**) 23, 163-178.

6) **Y Mahé**, J P Piau, N Wakasugi, T Tursz, G. Gacon & H Wakasugi: Comparison of Interleukin-2 and 12-O-tetradecanoyl-phorbol-13-acetate as signals for protein kinase C activation in purified human T lymphocytes. European J. Immunol. (**1988**) 18, 2029-2036.

7) **Y Mahé**: Mécanismes d'activation des cellules lymphocytaires T: Rôle du calcium, des Interleukines et activation des protéines kinases. Thèse de Doctorat de l'Université de Paris VI, spécialité: Pharmacologie (**1988**).

8) K Matsushima, M Shiroo, **Y Mahé** & N Mukaida: Molecular analysis of the induction of Interleukin-8 gene by Interleukin-1 (IL-1), Tumor Necrosis Factor (TNF) and phorbol ester. in Molecular and cellular biology of cytokines, JJ Oppenheim, MC Powanda, MJ Kluger & CA Dinarello Eds., Wiley Liss Inc. Publ. New York (**1990**) 333-338.

9) S Bailly, **Y Mahé**, B Ferrua, H Wakasugi, T Tursz & MA Gougerot-Pocidalo: Ciprofloxacin differentially modulates IL-1α and IL-1β production. in Molecular and cellular biology of cytokines, JJ Oppenheim, MC Powanda, MJ Kluger & CA Dinarello Eds., Wiley Liss Inc. Publ. New York (**1990**) 93-98.

10) S Bailly, **Y Mahé**, B Ferrua, M Fay, T Tursz, H Wakasugi & MA Gougerot-Pocidalo: Quinolone-induced differential modification of IL-1α and IL-1β production by LPS-stimulated human monocytes. Cellular Immunol. (**1990**) 128, 277-288.

11) N Mukaida, **Y Mahé** & K Matsushima: Cooperative interaction of NFκB and C/EBP-like factor binding elements in activation of the Interleukin-8 gene by pro-inflammatory cytokines. J. Biol. Chem. (**1990**) 265 21128-21133.

12) **Y Mahé**, H Wakasugi, C Scamps, S Chouaib & T Tursz: Role of calcium on Interleukin-1 production by monocytes: its relevance during T-cell proliferation. Lymphokines and Cytokines Research (**1991**) 10, 165-172.

13) S Chouaib, **Y Mahé**, S Mechri, M Anndreff & K Welte: Differential sensitivity of CD4+ and CD8+ T-lymphocytes to phorbol Myristate acetate upon anti-CD3 stimulation: Evidence for a distinct signaling pathway. International J. Immunopathol. Pharmacol. (**1991**) 4, 19-32.

14) **Y Mahé**, N Mukaida, K Kuno, M Akiyama, N Ikeda, K Matsushima & S Murakami: Hepatitis B virus X-protein transactivates human interleukin-8 gene through acting on nuclear factor κB and CCAAT/enhancer-binding protein-like cis-elements. J.Biol. Chem. (**1991**) 266, 13759-13763.

15) C Pique, **Y Mahé**, C Scamps, C Tetaud, T Tursz & J Wiels: Analysis of phenotypic and functional changes during gangliosides-induced inhibition of human-T-cell proliferation. Molecular Immunol. (**1991**) 28, 1163-1170.

16) **Y Mahé**, N Mukaida & K Matsushima: Mechanisms of IL-8 gene regulation by Tumor Necrosis Factor and Interleukin-1. in Tumor Necrosis Factor: Structure-Functions Relation-ship and Clinical Application. B Buonavida & T Osawa Eds., Karger Publ. Basel (**1992**) 152-158.

17) **Y Mahé** & JJ Oppenheim: Interleukin-1 in Encyclopedia of Immunology. I M Roitt & P Delves Eds. Saunders Publ. New York (**1992**) 897-901.

18) **Y Mahé**, K Hirose, B Clausse, T Tursz, S Chouaib & B Mariamé: heterogeneity among human nasopharyngeal carcinoma cell lines for inflammatory cytokines mRNA expression levels. Biochem. Biophys. Res. Comm. (**1992**) 187, 121-126.

19) A Zyad, D Branellec, **Y Mahé**, T Tursz & S Chouaib: The development of human tumor-cell resistance to TNFα does not confer resistance to cytokine-induced cellular cytotoxic mechanisms. Int. J. Cancer (**1992**) 52, 953-958

20) Y Mahé, L Breton, JB Galey & B Bernard. Patent. FR 9411133 du 19/09 (**1994**): « Utilisation de 2,4-diamino pyrimidine 3-Oxyde ou de l'un de ses sels dans le traitement des désordres de la maturation et de la structuration du collagène ». *Extension WO9609048*: Use of 2,4-diamino-pyrimidine-3-oxyde to treat collagen disorders-involving collagen maturation and structuring, e.g. vitreo-retinopathy, systemic scleroderma and keloïds, without hypotensive effects.

21) F Vecchini, K Mace, J Magdalou, **Y Mahé**, B Bernard & B Shroot: Constitutive and inducible expression of drug metabolizing enzymes in cultured human keratinocytes. British J. Dermatol. (**1995**) 132, 14-21.

22) Y Mahé, N Billoni & JF Michelet. Patent FR 9501880 du 17/02 (**1995**): « Test de matières actives sur cheveux épilés ».

23) Y Mahé, B Buan & G Loussouarn. Patent 9501881 du 17/02 (**1995**): « Procédé pour diagnostiquer et/ou suivre l'évolution d'un désordre capillaire et/ou mesurer l'éfficacité d'un traitement appliqué pour combattre un désordre capillaire ».

24) JF Michelet, **Y Mahé** & B Bernard. Patent FR 9504049 du 5/04 (**1995**): « Utilisation dans une composition en tant qu'activateur et/ou stabilisateur de cyclooxygénase d'au moins un dérivé de pyrimidine substitué en 6 ».

25) Y Mahé. Patent FR9505158 du 28/04 (**1995**): « Utilisation de dérivés de l'hormone stimulatrice des mélanocytes de type alpha pour stimuler ou induire la pousse des cheveux et/ou stopper leur chute ». Drug for promotion or stimulation of hair growth contains tripeptide comprising lysine, proline and valine.

26) Y Mahé & B Buan. Patent FR9510977 du 19/09 (**1995**): « Utilisation d'au moins un peptide dans une composition cosmétique ou pour la préparation d'un médicament ».

27) B A Bernard, S Commo, C Gerst, **Y Mahé**, F Pruche: Données récentes sur la biologie du cheveu. BEDC (**1996**) 4, 55-64.

28) G Courchay, N Boyera, B Bernard & **Y Mahé**: Messenger RNA expression of steroïdogenesis enzyme subtypes in the human pilo-sebaceous unit. Skin Pharmacol . (**1996**) 9 (3):169-176.

29) **Y Mahé**, B Buan & B Bernard : A Minoxidil-related compound lacking a C6 substitution still exhibits strong anti-Lysyl hydroxylase activity in vitro Skin Pharmacol. (**1996**) 9 (3):177-183.

30) **YF Mahé**, B Buan, N Billoni, J-F Michelet and B A Bernard: Inflammatory cytokines cascade in the pilosebaceous unit: Interleukin-1 as putative co-actor of androgenetic alopecia ? In "Hair research for the next Millenium" D.V. Neste & V.A. Randall Eds.; Elsevier Publisher 453-456 (**1996**).

31) **YF Mahé**, B Buan, N Billoni, G Loussouarn, J-F Michelet, B Gautier and BA Bernard. Pro-inflammatory cytokines cascade in human plucked hair . Skin Pharmacol. (**1996**); 9 (6): 366-375.

32) J-F Michelet, S Commo, N Billoni, **YF Mahé** and BA Bernard. Activation of the cytoprotective Prostaglandin Synthase-1 by minoxidil as a possible explanation of its hair growth effect. J. Invest. Dermatol (**1997**); 108 (2):205-209.

33) Y. F. Mahé, G. Loussouarn, F.Rimek, B.Buan, B. A. Bernard: L'interleukine-1, co-acteur possible de l'alopécie androgénétique. Hair & Sciences (**1997**) 3 (3): 16-18 .

34) N Billoni, B Gauthier, **YF Mahé** and BA. Bernard. Expression of retinoid nuclear receptor superfamily members in human hair follicle and its implication on hair growth. J. Venereol. Dermatol. (**1997**); 77:350-355

35) J-B. Galey, **Y. Mahé**, B. Bernard, L. Breton and G. Loussouarn. Research and development of a new anti-hair loss molecule:2,4 DPO or Aminexil®. Proceedings of IFSCC International conference, September 1997, Acapulco, Mexico GL Mendoza ed. (**1997**) ; 259-269.

36) **YF Mahé**, BA Bernard. Structure et Biologie du Cheveu. Biologie de la peau humaine. D. Schmidt ed. Editions INSERM (**1997**); 137-148.

37) YF Mahé, Inflammatory perifollicular fibrosis and alopecia. International J Dermatol (**1998**). 37: 5-7

38) YF Mahé, JF Michelet, N Billoni, F Jarrousse, B Buan, S Commo, D St Leger and BA Bernard. A review on inflammation in androgenetic alopecia: is there a rationale to consider inflammation in androgenetic alopecia. International J Dermatol (**1998**) in press

39) N. Boyera, **Y. Mahé**, L.Breton, I. Galey, B.Buan, S.Commo, B.A. Bernard. 2,4 DPO, a novel anti-hair loss agent for the treatment of androgenetic alopecia (to be submitted).